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Blueberries – a hyperberry for hypertension.

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Hypertension: *the problem*

- ▶ BP \geq 140/90 mm Hg (Canadian Hypertension Education Program; American Heart Association)
- ▶ a major risk factor for heart attack, stroke, kidney disease
- ▶ worldwide prevalence ~26% of adults, 1 B people (Savica et al. 2010); **~29% of US adults (+31% are pre-hypertensive)**
- ▶ Costs ~\$60B in US and \$300M in Canada
- ▶ a reduction in BP of only 3mmHg may reduce mortality by 5–8% (Padwal et al. 2005)






walking the way to health

“Lifestyle modification, although often neglected, is an important strategy to prevent and treat hypertension and reduce anti-hypertensive drug burden”.

CHEP Recommendations, 2005

Table 1: Blood pressure reductions achieved with lifestyle interventions

Intervention	Mean blood pressure reduction, mm Hg (95% CI)	
	Systolic	Diastolic
Weight loss (per kg lost)	1.1 (0.7–1.4)	0.9 (0.6–1.3)
DASH diet ¹		
Hypertensive patients*	11.4 (7.0–16.0)	5.5 (2.7–8.2)
Normotensive patients	3.5 (1.6–5.3)	2.1 (0.5–3.6)
Sodium restriction (maximum 78 mmol or 1.8 g daily)		
Hypertensive patients	5.0 (4.2–5.8)	2.7 (2.3–3.2)
Normotensive patients	2.0 (1.5–2.6)	1.0 (0.6–1.4)
Potassium supplementation (50 mmol or 1.9 g daily)		
Hypertensive patients	4.4 (2.2–6.6)	2.5 (0.1–4.9)
Normotensive patients	1.8 (0.6–2.9)	1.0 (0.0–2.1)
Aerobic exercise (120–150 min/wk of walking, jogging or biking)		
Hypertensive patients	4.9 (2.7–7.2)	3.7 (1.8–5.7)
Normotensive patients	4.0 (2.8–5.3)	2.3 (1.5–3.1)
Alcohol restriction (from 3–6 drinks to 1–2 drinks per day)		
Hypertensive patients	3.9 (2.7–5.0)	2.4 (1.6–3.3)
Normotensive patients	3.6 (2.5–4.6)	1.8 (0.6–3.3)

¹Hypertensive patients have a blood pressure of $\geq 140/90$ or higher.

Box 1: The Dietary Approaches to Stop Hypertension (DASH) eating plan*

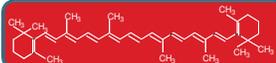
Food group (examples or comments)	Recommended no. of daily servings
Grains (whole wheat bread, oatmeal)	7–8
Vegetables (tomatoes, potatoes, carrots, beans, spinach, peas, squash)	4–5
Fruits (bananas, grapes, oranges, apricots, apples)	4–5
Low-fat dairy products (fat-free (skim) or low-fat (1%) milk, yogurt, cheese)	2–3
Meats (primarily poultry or fish; select lean meats and prepare by trimming fat and broiling, roasting or boiling. Remove skin from poultry)	≈ 2
Nuts, seeds, dry beans (peanuts, walnuts, almonds, sunflower seeds, lentils)	4–5/week
Fats and oils (soft margarine, vegetable oil (e.g., olive, corn, canola or safflower))	2–3
Sweets (apple syrup, sugar, jam, jelly, hard candy, sorbet)	≤ 5/week

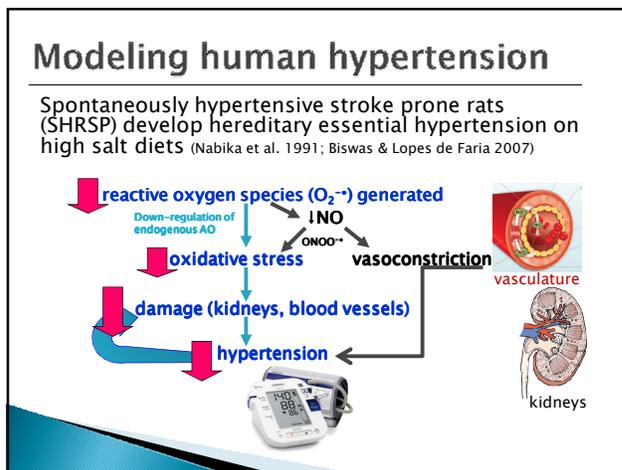
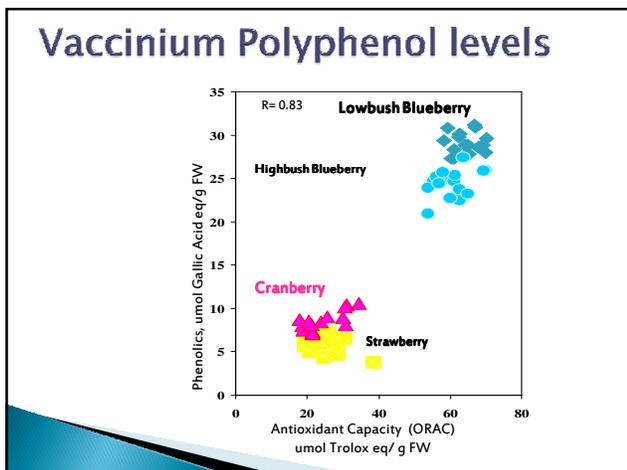
*The DASH Eating Plan is available at www.nhlbi.nih.gov/health/public/heart/hypertol/dash.htm.

Vaccinium angustifolium

- Member of heath family (Ericaceae). Lowbush variety in N.E. North America grow 'wild'.
- Shoots emerge in the spring, flower, pollinated by bees, and fruit 2–3 months later.
- Contain many polyphenolic compounds, esp **flavonoids**:
 - >20 different **anthocyanins** ([Matchett et al. 2005]; structurally similar to tea flavanols [Manach & Donovan 2004])
 - Large proanthocyanidins** (condensed tannins [Matchett et al. 2005])
- Mitigate oxidative stress.
- Have other bioactivities e.g. anti-inflammatory.







Are antioxidants beneficial in hypertension?



- ▶ Dietary fruits & vegetables/DASH lower BP (Savica et al. 2010).
- ▶ Pharmacological doses of vitamin C \Rightarrow vasodilation \Rightarrow \downarrow blood pressure, although results from some studies have been inconclusive or disappointing (Rodrigo et al. 2007).
- ▶ Quercetin, a highly abundant flavonol, \Rightarrow long-lasting anti-hypertensive effects in several animal models of hypertension, as well as in humans (Perez-Vizcaino et al., 2009).
- ▶ Tea catechins are good vasodilators and \downarrow BP and \uparrow life span in SHRSP (Uchida 1995; Negishi et al. 2004).
- ▶ Anthocyanins \uparrow NO and \downarrow BP (Savica et al. 2010).
- ▶ Foods rich in flavanols and procyanidins, such as cocoa, \downarrow BP (Ghosh and Scheepens, 2009; Savica et al., 2010).

Effect of *Vaccinium* berries on BP



3% freeze-dried blueberry powder in AIN 93 diet



8 wk old SHSP rats or WKY controls

3% Nutricran[®] organic cranberry powder

Methods: SHRSP

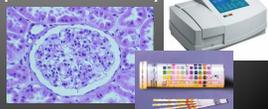
1) Blood pressure :

- ▶ fed control AIN diet or 3% blueberry or cranberry diet + 2% NaCl
- ▶ Week 2, 4, 6, 7, 8: **systolic BP** measured using tail cuff method
- ▶ Monitored for SRS



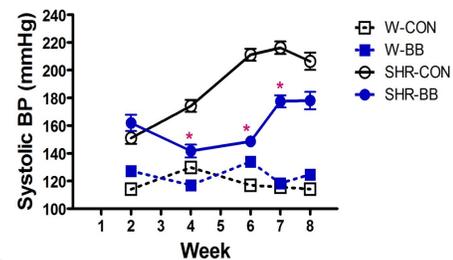
2) Renal pathology :

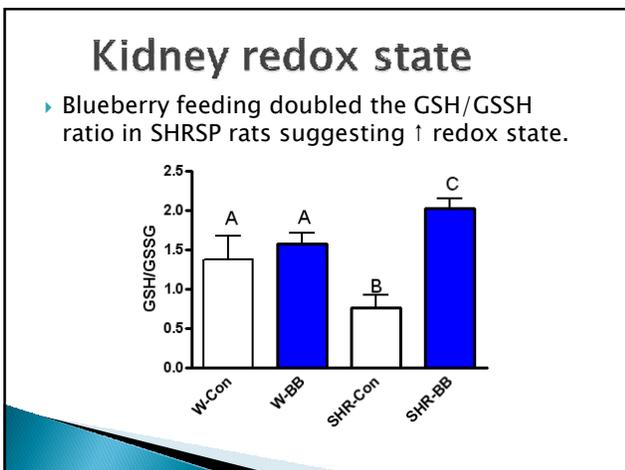
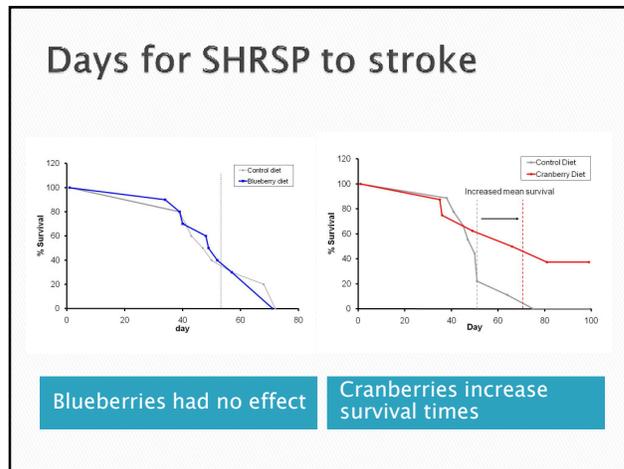
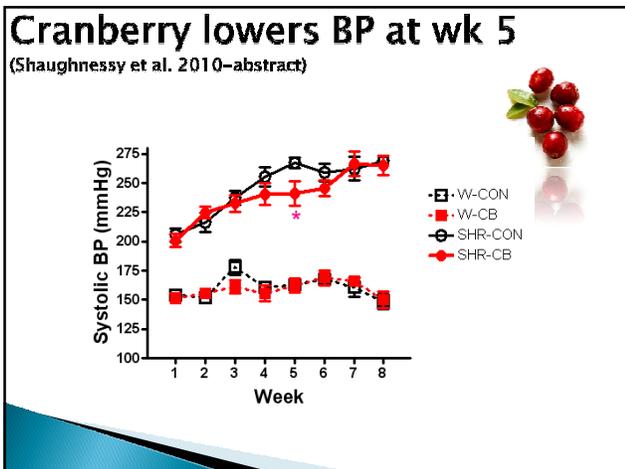
- ▶ fed control AIN diet or 3% blueberry diet + 2% NaCl
- ▶ Week 16: urinalysis
- ▶ Week 17: euthanasia; one kidney fixed for histology; one kidney flash-frozen for glutathione measurement spectro-photometrically



Blueberries lower BP at wk 4-7

(Shaughnessy et al. 2009)





Kidney pathology

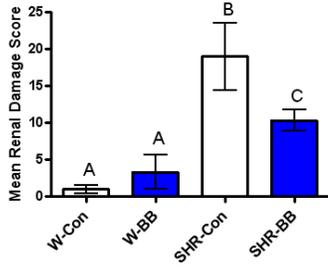
SHRSP rats on control diets had renal damage:

- ▶ Bowman's capsule thickening
- ▶ glomerular sclerosis and obsolescence
- ▶ arcuate artery and renal arteriole myointimal hyperplasia
- ▶ renal vascular thrombosis

Blueberry feeding reduced or eliminated all of these pathologies (except renal arteriole myointimal hyperplasia).

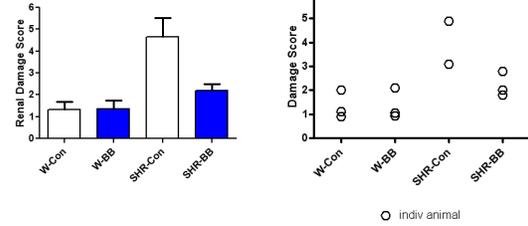
Kidney pathology (overall)

Blueberry fed SHSP rats had less renal damage than control fed rats ($p = 0.002, N=3$).



Kidney pathology: individual markers

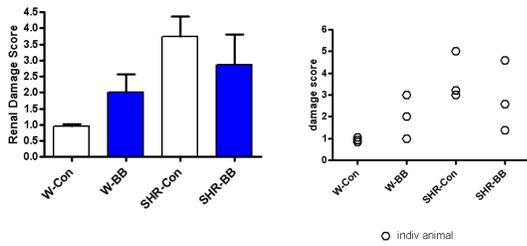
Glomerular Sclerosis¹



1. fibrosis & scarring of the renal glomeruli; early hypertensive changes.

Kidney pathology: individual markers

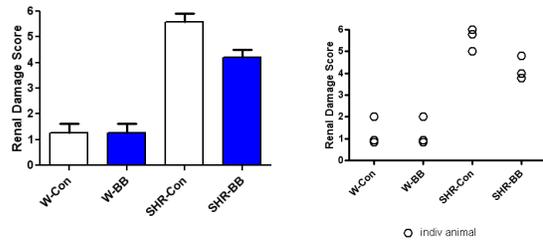
Arcuate artery myointimal hyperplasia²



2. migration and proliferation of vascular smooth muscle cells in response to injury

Kidney pathology: individual markers

Tubular protein³



3. slight protein is normal in urine; excess implies leaking in glomeruli.

Urinalysis results

- Urine from blueberry fed SHSP had slightly less leukocytes and 60% less protein content than SHSP rats on normal diets (N=3).

	Leukocytes	Protein
Control rats, normal diet	-	+ (10 ± 10)
Control rats, BB diet	-	+ (10 ± 10)
SHSP rats, normal diet	+++ (1.67 ± 0.33)	+++++ (366.7 ± 133.3)
SHSP rats, BB diet	++ (1.33 ± 0.17)	++ (150 ± 50)

Flavon-3-ols (and food containing them) are ACE inhibitors (Actis-Goretti et al. 2006; J. Agric. Food Chem. 54: 229-234.)

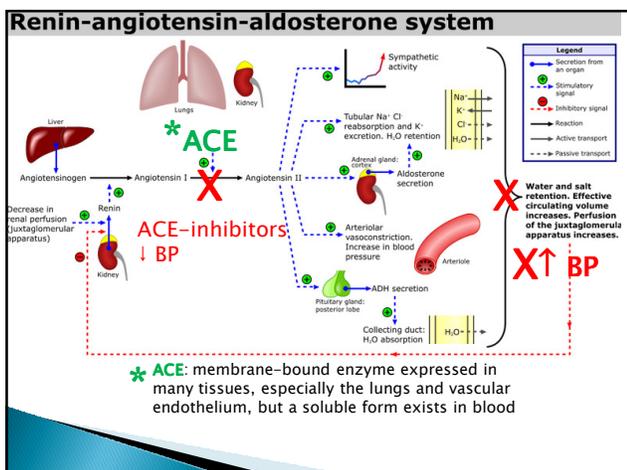
Inhibition of Angiotensin Converting Enzyme Activity by Flavanol-Rich Foods

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Physical Chemistry-PRALIB, School of Pharmacy and Biochemistry, University of Buenos Aires, Argentina, Junin 956, 1113 Buenos Aires, Argentina, and Department of Nutrition, University of California, One Shields Avenue, Davis, California 95616-5270

Angiotensin converting enzyme (ACE) activity was evaluated in the presence of flavanol-rich foods, i.e., wines, chocolates, and teas, and of purified flavonoids. All foods assayed inhibited ACE activity, red wines being more effective than white wine, and green tea more effective than black tea. The inhibition of ACE activity was associated with both phenolic and flavanol content in the foods. When isolated polyphenols were assayed, procyanidins (dimer and hexamer) and epigallocatechin significantly inhibited enzyme activity; similar concentrations of (+)-catechin, (-)-epicatechin, gallic acid, chlorogenic acid, caffeic acid, quercetin, kaempferol, and resveratrol were ineffective. When ACE activity was assayed in rat kidney membranes in the presence of chocolate extracts or purified procyanidins, it was observed that the inhibition depended on the chocolate content of flavanols and the number of flavanol units constituting the procyanidin. These experiments demonstrate that flavanols either isolated or present in foods could inhibit ACE activity. The occurrence of such inhibition in vivo needs to be determined, although is supported by the association between the consumption of flavanol-rich foods and reductions in blood pressure observed in several experimental models.

KEYWORDS: Flavanol-rich foods; flavanols; procyanidins; angiotensin converting enzyme



Hypertension CANADA

TABLE 3: CONSIDERATIONS IN THE INDIVIDUALIZATION OF ANTIHYPERTENSIVE THERAPY: ACE INHIBITORS; CONVERTING ENZYME; TIA TRANSIENT ISCHEMIC ATTACK; ARE ANGIOTENSIN RECEPTOR BLOCKER

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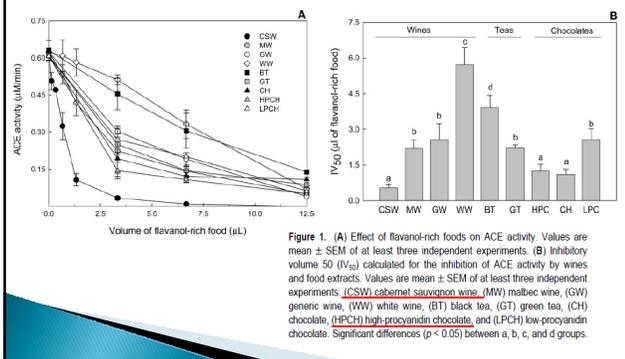
HYPERTENSION WITHOUT OTHER COMPELLING INDICATIONS

Diastolic/systolic hypertension	Thiazide diuretics, beta-blockers, ACE inhibitors, ARBs, or long-acting calcium channel blockers (consider ASA and statins in selected patients)	Combinations of first-line drugs	Beta-blockers are not recommended as initial therapy in those over 60 years of age. Hypokalemia should be avoided by using potassium-sparing agents in those who are prescribed diuretics as monotherapy. ACE inhibitors are not recommended in blacks. ACE inhibitors and ARBs are teratogenic and marked caution is required if prescribing to women of child bearing potential.
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DIABETES MELLITUS

Diabetes mellitus with nephropathy	ACE inhibitors or ARBs	Addition of thiazide diuretics, cardioselective beta-blockers, long-acting calcium channel blockers or use an ARB/ACE combination	If the serum creatinine level is >150 mmol/L, a loop diuretic should be used as a replacement for low-dose thiazide diuretics if volume control is required
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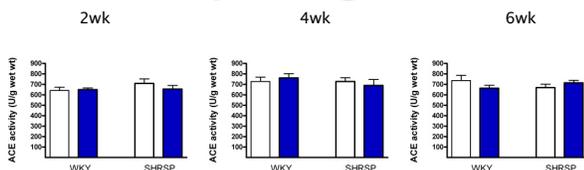
Flavon-3-ols (and food containing them) are ACE inhibitors (Actis-Goretta et al. 2006; J. Agric. Food Chem. 54: 229-234.)



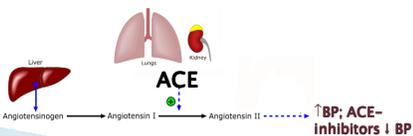
Our study methods

- male WKY (n=24) and SHRSP (n=24) aged 7 wk acclimated for 1 wk, and then randomly assigned to a diet:
 - (1) AIN '93G purified diet + 3% freeze-dried blueberry or
 - (2) AIN '93G purified diet lacking BB (control)
- blood taken every 2 weeks
- tissues removed after 6 weeks
- ACE activity determined by colorimetric assay (ALPCO Diagnostics)

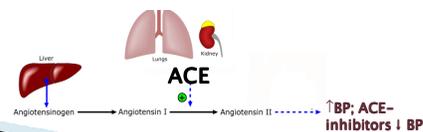
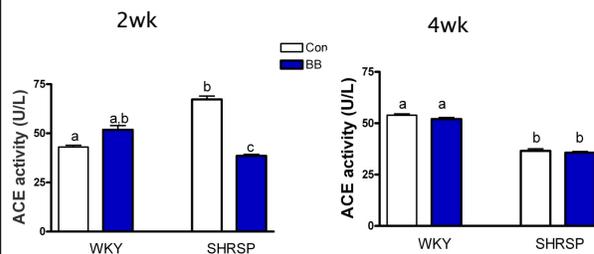
ACE activity in lung (Wiseman et al. 2011)



Same trend in other ACE-rich tissues e.g. kidney, testis, blood vessels.



ACE activity in serum (Wiseman et al. 2011)



Summary

In spontaneously hypertensive stroke prone rats, feeding blueberries appears to:

- ▶ slow the development of hypertension
- ▶ reduce the severity of hypertension
- ▶ prevent early renal pathologies and increase the redox state of the kidney; inhibit soluble but not tissue ACE: *likely mechanisms for the beneficial effects on hypertension.*
- ▶ Cranberries prolong survival in SHRSP

